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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,694	08/13/2001	Jan C. Simon	24741-1525	1918

26633 7590 02/26/2004

HELLER EHRMAN WHITE & MCAULIFFE LLP
1666 K STREET,NW
SUITE 300
WASHINGTON, DC 20006

EXAMINER	
DAVIS, RUTH A	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,694	SIMON ET AL.	
	Examiner	Art Unit	
	Ruth A. Davis	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-54 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-54 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Appeal Brief has been received and entered into the case. As the Valavicius reference has been provided and translated in full, this Office action is Non-Final. All arguments presented have been fully considered. Claims 36 – 54 and 56 are pending and have been considered on the merits.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 36 – 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over The Hypericum Homepage (Hypericum & Depression, Bloomfield et al., copyright 1996, Prelude Press, Editor J. Sedillos – copy made available from hypericum.com) in view of The Merck Manual (1995-2002).

Applicant claims a method for treating a condition selected from cancer, inflammatory skin diseases, precancerous conditions, geriatric skin or microbial skin infections comprising topical administration of an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) an active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, to a subject in need thereof. Specifically, the condition is eczema, or is selected from exsiccation eczemas, hyperkeratotic hand/foot eczemas, contact eczemas, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphoma, leukemia, melanoma, epithelial precancerous conditions, tumor metastases or epithelial tumors. The subject is a mammal and the composition is a topical ointment with an effective amount of at least 15 micrograms hyperforin per ml, 0.02 – 20 mg/ml, 1 – 20 mg/ml or 10 mg/ml; or 15 micrograms/ml or 20 – 150 micrograms/ml hypericin.

The Hypericum Home Page (HHP) teaches extracts of Hypericum perforatum (St. John's Wort) include hypericin and hyperforin wherein the extracts exhibit anti-inflammatory and antibacterial effects when externally, or topically, applied (p.3). HHP specifically teaches that hyperforin is attributed with anti-inflammatory and antibacterial effects (p.3).

HHP does not teach a method for treating an inflammatory condition with the claimed effective amounts or the claimed specified conditions. However at the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to use hyperforin and/or

hyperforin and hypericin in a method for treating inflammatory conditions because of the disclosed anti-inflammatory effect. Furthermore, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize effective volumes and concentrations as a matter of routine experimentation. It would have been further obvious to one of ordinary skill in the art to include a pharmaceutical carrier because it was routine practice in the art at the time the claimed invention was made. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to use hyperforin in a method for treating external anti-inflammatory conditions with a reasonable expectation of success because of its known anti-inflammatory activity as disclosed by HHP.

HHP does not specifically teach the extracts are effective against eczema, or the other conditions as claimed. However, at the time of the claimed invention, it was well known in the art that eczemas are characterized by inflammation (see "The Merck Manual", previously provided). Specifically, eczema, contact eczema, atopic eczema, hand and foot eczemas, and lichen simplex are each characterized as superficial inflammations of the skin of varying degrees. In further support, Shroot et al. teaches inflammatory diseases include dermatitis and eczema (col.1 line 12-15) and Lacefield teaches inflammatory conditions include atopic dermatitis, contact dermatitis, eczema, lichen simplex and chronic dermatoses. At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to treat any of the aforementioned eczemas with hyperforin because of the anti-inflammatory effect as disclosed by HHP. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by HHP and Merck to utilize hyperforin in a method for treating inflammation and eczemas with a reasonable expectation for success.

Applicant argues that HHP is not a valid prior art reference, specifically prior to Applicant's foreign priority date of November 25, 1998. Applicant additionally argues that even though HHP does teach hyperforin has anti-inflammatory and antibacterial effects, the reference teaches externally applying St. John's Wort, not hyperforin. Applicant further argues that HHP does not teach the claimed method of treating the claimed conditions with a purified, effective amount of hyperforin in a carrier; that it is unclear if the hyperforin causes or treats the inflammation; that there is no motivation to use hyperforin in a method for treating inflammatory skin conditions; and that Merck does not provide motivation to use hyperforin in any skin inflammatory condition.

However, these arguments fail to persuade because as stated in previous office actions, 35 U.S.C 102 states the conditions for patentability; novelty and loss of right to patent:

> A person shall be entitled to a patent unless -
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent, or
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States,

MPEP section 2132 states that "Known or Used" Means Publicly Known or Used. "The statutory language known or used by others in this country' (35 U.S.C. § 102(a)), means knowledge or use which is accessible to the public." The knowledge or use is accessible to the public if there has been no deliberate attempt to keep it secret. In addition, a prima facie case is made out under 35 U.S.C. 102(a) if, within 1 year of the filing date, the invention, or an obvious variant thereof, is described in a "printed publication" whose authorship differs in any way from the inventive entity unless it is stated within the publication itself that the publication is

describing the applicant's work. MPEP section 2128 – 2128.02 states that a reference is a printed publication if it is accessible to the public. A reference is proven to be a "printed publication" "upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it."

In the instant case, the HHP reference clearly has a copyright date of 1996. Thus, the reference was accessible to the public, there was no deliberate attempt to keep it secret and the document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it. As such, the reference qualifies as prior art under both 35 USC 102 (a) and (b). Regarding applicant's assertion that it is unclear if the reference was part of the HHP website, the pages provided state that the disclosure is excerpted the ESCOP, as well as being part of the book "Hypericum & Depression" with a copyright of 1996. Moreover, the reference is the same as if making photocopies of the book itself.

Regarding the effects of hyperforin, applicant admits that HHP teaches hyperforin is attributed with both anti-inflammatory and antibacterial activity when St. John's Wort is externally applied. Although the reference does not teach the claimed method of applying hyperforin in a carrier to treat the claimed skin conditions, HHP clearly teaches hyperforin is an effective anti-inflammatory and antibacterial agent. As such, at the time of the claimed invention, one of ordinary skill in the art would certainly have been motivated by HHP to treat external inflammatory/microbial conditions with hyperforin. In addition, as stated above, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to

incorporate the known active agent, hyperforin, into a carrier, and optimize the effective amounts as a matter of routine practice and experimentation in the art. As to Merck and the supporting references, these references are relied upon to demonstrate that the claimed conditions were well known in the art as inflammatory and microbial skin conditions. Therefore, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to treat the claimed skin conditions with hyperforin, with a reasonable expectation of success.

4. Claims 36, 38 – 43, 46 – 49 and 56 rejected under 35 U.S.C. 103(a) as being unpatentable over Valavicius (892 – document U).

Applicant claims a method for treating a condition selected from cancer, inflammatory skin diseases, precancerous conditions, geriatric skin or microbial skin infections comprising topical administration of an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) an active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, to a subject in need thereof. The condition is selected from exsiccation eczema, hyperkeratotic hand and foot eczema, contact eczema, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphoma, leukemia, melanoma, epithelial precancerous conditions, tumor metastases or epithelial tumor. The subject is a mammal. Applicant additionally claims a method of treating cancer comprising administering to a subject in need thereof an effective amount of a composition comprising hyperforin and a pharmaceutically acceptable carrier. The effective amount comprises at least 50 micrograms hyperforin/ml in an injectable form, 100

micrograms/microliter suitable for epicutaneous application, 50 micrograms/ml for systemic administration. The hyperforin is at least 90% pure.

Valavicius teaches extracts of St. John's Wort, specifically oil extracts, inhibits growth of sarcoma cells (abstract) and tumors in various organs in rats (p.1-3 translation). Specifically, Valavicius teaches that intraperitoneal administration of the extracts at 0.25, 0.50, 1.0 and 2.0 mg/kg inhibits growth of tumors in animals (or subjects in need thereof) (p.2-3 translation). At the time the claimed invention was made, it was known in the art that oil preparations of St. John's Wort are hypericin free and contain high concentrations of hyperforin (See Chavez, p.1622) and that intraperitoneal administration typically contains pharmaceutically acceptable carriers.

Valavicius does not teach the method wherein the claimed volumes and concentrations were used, modes of administration, or wherein the hyperforin is at least 90% pure. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize effective volumes, modes of administration and purity of known, effective agents as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the effective amounts of Valavichyus with a reasonable expectation for successfully treating cancer.

Applicant argues that Valavicius does not expressly teach administering only St. John's Wort oil, but may teach a combination of St. John's Wort and Chamomilla. Applicant argues that it is not clear if the oil contained additional components, as the method of making the oil is

not disclosed; that since the plant contains many active agents, it is unclear if hyperforin is acting in the tumor inhibition; that Chavez cannot be relied upon since the reference does not teach specific amounts of hyperforin in the oil; and that the references do not teach the purity of hyperforin or inclusion of carriers. Finally, applicant argues that impermissible hindsight is applied, that Valavicius teaches away from the claimed invention.

However, these arguments fail to persuade because Valavicius specifically teaches activity of St. John's Wort extracts alone and made in accordance with the teachings of Chavez. Although Chavez does not specifically teach an amount of hyperforin present, the extracts are certainly taught to contain high amounts of hyperforin. As such, at the time of the claimed invention, one of ordinary skill in the art would have reasonably attributed the anti cancer effects to hyperforin in the extracts. Regarding the carriers, at the time of the claimed invention, it was well known in the art that intraperitoneal administration typically contains pharmaceutically acceptable carriers. In addition, it is reiterated that at the time of the claimed invention, one of ordinary skill in the art would have been motivated to optimize the amounts of known effective ingredients as well as their purity, as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by Valavicius to treat cancer with hyperforin with a reasonable expectation of success.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the

applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

5. Claims 36, 38 – 54 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valavicius, HHP and DeCosterd (Helvetica Chimica Acta, 1989, vol.72, p.464-471).

Applicant claims a method for treating a condition selected from cancer, inflammatory skin diseases, precancerous conditions, geriatric skin or microbial skin infections comprising topical administration of an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) an active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, to a subject in need thereof. Specifically, the condition is selected from eczema, exsiccation eczema, hyperkeratotic hand and foot eczema, contact eczema, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphoma, leukemia, melanoma, epithelial precancerous conditions, tumor metastases or epithelial tumor. The subject is a mammal, and the composition is a topical ointment and the effective amount is at least 15 micrograms hyperforin per ml, 0.02 – 20 mg/ml, 1 – 20 mg/ml, 10 mg/ml, at least 15 micrograms hypericin/ml or 20 – 150 micrograms hypericin/ml. Applicant additionally claims a method of treating cancer comprising administering to a subject in need thereof an effective amount of a composition comprising hyperforin and a pharmaceutically acceptable carrier. The effective amount comprises at least 50 micrograms hyperforin/ml in an injectable form, 100 micrograms/microliter suitable for epicutaneous application, 50 micrograms/ml for systemic administration. The cancer

is melanoma, lymphoma, skin cancer, mammary carcinoma or leukemia carcinoma and the hyperforin is at least 90% pure.

Valavicius teaches extracts of St. John's Wort, specifically oil extracts, inhibits growth of sarcoma cells (abstract) and tumors in various organs in rats (p.1-3 translation). Specifically, Valavicius teaches that intraperitoneal administration of the extracts at 0.25, 0.50, 1.0 and 2.0 mg/kg inhibits growth of tumors in animals (or subjects in need thereof) (p.2-3 translation). At the time the claimed invention was made, it was known in the art that oil preparations of St. John's Wort are hypericin free and contain high concentrations of hyperforin (See Chavez, p.1622) and that intraperitoneal administration typically contains pharmaceutically acceptable carriers.

Valavicius does not teach the method wherein the claimed volumes and concentrations were used, modes of administration, or wherein the hyperforin is at least 90% pure. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize effective volumes, modes of administration and purity of known, effective agents as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by Valavichyus and routine practice to optimize the effective amounts of hyperforin with a reasonable expectation for successfully treating cancer.

Valavicius does not teach the method wherein the cancer is melanoma, lymphoma, skin cancer, mammary carcinoma and leukemia carcinoma. However, HHP teaches extracts of Hypericum perforatum (St. John's Wort) include hypericin and hyperforin wherein the extracts demonstrate anticancer properties and have been proven to inhibit tumor cells of the brain, lung

and skin (p.4). In addition, DeCosterd teaches extracts of Hypericum inhibit growth of colon carcinomas (abstract). Specifically, DeCosterd teaches derivatives of hyperforin exhibit the growth-inhibiting activity (abstract). At the time of the claimed invention, hypericin, hyperforin, derivatives thereof and extracts of Hypericum were well known as effective agents against cancers of various kinds, as evidenced by the cited references. Although HHP and DeCosterd do not specifically teach methods for treating cancer, the references certainly teach hypericin and hyperforin exhibit anti cancer activity. As such, one of ordinary skill in the art would have been motivated to treat cancers (i.e. lymphoma, mammary and leukemia carcinomas) with hypericin and hyperforin because of the demonstrated effectiveness in doing so in a variety of cancers. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by Valavicius, HHP and DeCosterd to treat various cancers with hyperforin or hyperforin and hypericin with a reasonable expectation of success.

Applicant argues that DeCosterd does not remedy the deficiencies of HHP or Valavicius as argued above. Specifically that DeCosterd teaches different compounds exhibiting inhibitory activity against carcinoma cells in vitro.

However, these arguments fail to persuade for the reasons stated above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth A. Davis whose telephone number is 571-272-0915. The examiner can normally be reached on M-H (7:00-4:30); altn. F (7:00-3:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ruth A. Davis; rad
February 20, 2004.

LEON B. LANKFORD, JR.
PRIMARY EXAMINER